Claims 11-13, 17-19, and 21 are directed to compounds that have a complementary structure to a targeted RNA molecule and inhibit the function of the targeted RNA molecule. In order for a compound to have a complementary structure to a targeted nucleic acid, hydrogen bond donor and acceptor sites must be properly arranged to bind the targeted molecule. To this end, as will be further described below, the critical region of the targeted RNA molecule defines and limits the structure of the compound.

A. The Legal Standard.

The first paragraph of 35 U.S.C. § 112 sets forth the written description requirement for patents as follows:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The standard regarding what is or is not supported by the specification has been clearly articulated as requiring the specification to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the invention, i.e., whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 19 USPQ2d 1111, 1117 (Fed . Cir. 1991). Compliance with the written description requirement is essentially a fact-based inquiry that will "necessarily vary depending on the nature of the invention claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citing *In re DiLeone*, 436 F.2d

1404, 1405 (CCPA 1971)). Essentially, satisfaction of the written description requirement is determined on a case-by-case basis.

In *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993), the Federal Circuit upheld a Board determination that an appellant was not entitled to the benefit of the filing date of an earlier Israeli application based on the identification of partial DNA clones encoding a protein, where the clones had not been sequenced and the entire nucleotide molecule could not be predicted. As is well known in the industry, partial clones can contain concatamers, reversed sequence, missing portions, etc. so until the clones can be sequenced and the entire molecule constructed, amino acid sequence predicted and matched to actual amino acid sequence, one skilled in the art would not be able to make or use the DNA sequence.

In *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, (Fed. Cir. 1997), the Federal Circuit invalidated on written description grounds claims to any cDNA encoding a mammalian insulin on the basis that the only nucleotide sequence disclosed in the patent encoded rat insulin. The Court ignored evidence that one would be able to routinely obtain the other sequences, stating that "[a]n adequate written description of a DNA . . . 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." 119 F.3d at 1566 (quoting *Fiers*, 984 F.2d at 1171).

In the most recent CAFC decision, *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. Apr. 2, 2002), the Federal Circuit upheld a summary judgment of invalidity of a

patent claiming nucleic acid molecules that selectively hybridize to specific bacterial probes that had been deposited with the ATCC, even though the Patent Office had issued the patent based on compliance with *In re Lundak*, the MPEP, and evidence that the application complied with 35 U.S.C. §112, enablement. The Court emphasized that "[t]he disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim." *Enzo*, slip op. (citations omitted). Presumably, this case will be appealed and. at a minimum, clarification requested as to why the court did not hear any factual evidence to support its position. This would be in accordance with Judge Dyk's statements, in his dissent. Judge Dyk dissented from the opinion in *Enzo*, among other things, opining that the description of the invention in *Enzo* was more than merely functional. Judge Dyk's dissent also faults the majority for deciding the issue on summary judgment without a factual predicate. *Enzo*, slip op. (dissenting). The majority's analysis indeed provides no serious consideration of whether any of the alleged failings in the written description might be known to one skilled in the art, determining instead that the description was deficient as a matter of law. *Enzo*, slip op.

Judge Dyk refers to the Court's previous decisions in similar matters, requiring a consideration of the factural evidence.

> In *In re Alton*, 76 F.3d 1168, 1174-75, 37 USPQ2d 1578, 1583-84 (Fed. Cir. 1996), this court reversed a decision of the Patent and Trademark Office ("PTO") Board of Patent Appeals and Interferences ("Board") upholding an examiner's rejection of Alton's patent application for failure to comply with the written description requirement. Alton had submitted a declaration from one of ordinary skill in the art stating that one of ordinary skill in the art would have understood the specification as adequately describing the claimed invention. *Id.* at

> 1172-73, 37 USPQ2d at 1581-82. The examiner gave little or no weight to this declaration, contending that it was "an opinion affadavit on the ultimate legal question at issue." *Id.* at 1174, 37 USPQ2d at 1583. We reversed because the examiner and the Board applied the wrong legal standard by viewing the declaration as addressing a question of law rather than a question of fact, and required the PTO to evaluate the expert's affadavit as bearing on the factual issue. *Id.*

Enzo, slip op. (Dyk, J., dissenting). Alton thus makes clear that an examiner is required to consider affidavits regarding the understanding of one with ordinary skill in the art when evaluating the adequacy of a written description.

The inquiry into adequate written description is not performed in a vacuum. "Knowledge of one skilled in the art is relevant to meeting [the written description] requirement." *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. Apr. 2, 2002) (slip op.). This fact has implications not only for validity challenges, but also for patent prosecution. *See In re Alton*, 76 F.3d 1168, 1174-75 (Fed. Cir. 1996).

As will be discussed below, Applicant has not only provided significant structural and physical properties of the claimed compounds and their cognate RNA targets, Applicant has additionally submitted two independent expert opinions (in the form of declarations under 37 C.F.R. § 1.132) that clearly support this assertion and describe the specification as being sufficient for one of ordinary skill in the art to know the *structural* features that *define* the claimed compound.

B. The Specification and Claims define structural features.

The specification describes the structure of the claimed compounds by illustrating the chemical properties (hydrogen bond acceptor and donor sites arranged specifically) and method of preparation (first, determining the target RNA sequence and second, preparing the compounds accordingly) of the compounds. These features have now been incorporated into the claims. These elements distinguish the compounds based on the claimed interaction with a critical region in the minor groove of the target RNA. Although the compounds may be organic, inorganic, proteins, or even nucleic acids, specific binding is achieved through complementary interactions (page 38 of the specification, lines 24-31). These interactions are dependent upon hydrogen bonding (lines 29-17, bridging pages 38 and 39). Therefore, in order for the compound to bind to the target RNA, hydrogen bond donor sites, hydrogen bond acceptor sites, and chemical side groups, have to be in the correct spatial location, orientation, and have the correct charge. One of skill in the art would realize that it is this arrangement that defines the structure of the compound. "Complementary" defines the structure of the compound. Complementary compounds are limited by the sequence of the RNA target molecule. Given the minor groove sequence of the RNA to be targeted, the arrangement of possible hydrogen bonds to be utilized by the compound is defined, therefore limiting the structure of the compound.

As stated in M.P.E.P. § 2173.05(t), which describes the standard to be applied to compounds and compositions, "a compound of unknown structure may be claimed by a combination of physical and chemical characteristics." See *Ex parte Brian*, 118 USPQ 242 (Bd. App. 1958). M.P.E.P. § 2173.05(t) further states that "a compound may also be claimed in terms

of the process by which it is made without raising an issue of indefiniteness." It is important to note that only *after* obtaining the correct target RNA sequence, can the claimed compound and its structure be elucidated. This, however, is routine to those skilled in the art. The structural features common to the members of the claimed genus can only be determined once the hydrogen bonding arrangement of the target sequence is derived. Once the RNA sequence is derived, the minor groove structure can be easily inserted into any number of commercially available computer programs and the structural features of the compound determined. The structure of the compound is clearly limited based on the requirement for it to be complementary to the RNA sequence.

The complementary nature of the compound of base claim 11 distinguishes the claimed compound from others. Compounds that bind a RNA in the minor groove would not necessarily have the requisite correct charge and spatial orientation of the potential hydrogen bond donors and acceptors to be specific for presentation and binding to the targeted critical region of a RNA molecule. While most, if not all, compounds that bind RNA do have hydrogen bonding sites, only a few will have the necessary pattern of sites to be utilized specifically by the targeted critical region. The identification of the critical region within the minor groove by a combination of primary, secondary and tertiary structure analysis, as recited in claim 11, is required for the determination of the structure of the compound. Therefore the structural features common to the claimed compound, as defined by the term "complementary" and by containing the requisite hydrogen bonding acceptor and donor sites, are clearly described.

The specification also discloses other relevant information and identifying characteristics sufficient to describe the claimed invention. One of skill in the art would be able to predict the structure of the claimed complementary compound from the recitation of its function. It is well established that the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. The appellant respectfully submits that this correlation has been established as described above. The hydrogen bonding pattern of the compound defines the structure of the compound, however, this defining characteristic is at the mercy of RNA analysis as described in base claim 11.

C. Knowledge of those skilled in the art in relation to the present written description.

Submitted with this response are two declarations under 37 C.F.R. § 1.132 by Dr. Jules Rebek and Dr. James R. Williamson, respectively. Both Dr. Rebek and Dr. Williamson are experts in the field. Dr. Williamson has provided his expert opinion as well as enclosed data in support of the claims. The declarations are submitted in order to provide further evidence that the description of the structure of the critical region in the minor groove of RNA is sufficient to describe the structure of the claimed compound. Each declaration clearly elaborates upon the present specification's discussion of the forces presented in and by the targeted RNA molecule. While these forces establish the structure of the critical region of the RNA in terms of specific and available interactions and geometry, they are a direct result of the RNA sequence (primary

structure). Secondary and tertiary structures can subsequently be determined via any number of commercially available programs, as outlined in the declarations.

The analogy to a "lock and key", in the submitted declarations, is an important one because if one can conceptualize the role of the predetermined and defined target RNA in demanding a specific structure of the inhibitory compound, then one will realize that the compound structure is clearly defined. The target RNA is defined by those interactions and forces present in the minor groove of the critical region, as described in the specification, defined by the claims and further elaborated on by Drs. Jules Rebek and James R. Williamson.

The examiner's attention is drawn first to Dr. Rebek's declaration. Dr. Rebek is the Director of the Skaggs Institute of Chemical Biology and Professor of Chemistry of the Scripps Research Institute. Dr. Rebek is clearly an expert in the field of nucleic acid structure. Dr. Rebek has no personal or financial interest in this application. He was asked to review the specification and claims, in view of the legal standard for the written description under 35 U.S.C. §112, to determine if he, as one in the field, would know what the structure of the claimed compounds was, based on his knowledge, the specification, and the language of the claims. Dr. Rebek specifically addressed the structure of the minor groove of the RNA in responding, reviewing the hydrophobic environment of the minor groove, hydrogen bonding, electrostatic interactions, and geometric and steric constraints. As summarized on page 7, "All of these 'constraints' define the nature of the inhibitory compound in terms of structure and functionality;

they define the molecular recognition of the RNA by the compound where the compound is complementary in size, shape and chemical surface to the RNA."

The Examiner's attention is then drawn to Dr. Williamson's declaration. Dr. Williamson is a Professor of Molecular Biology and Chemistry at the Scripps Research Institute in La Jolla, CA. He is an expert in the field of RNA and drug design, including RNA structure, RNA-protein recognition, and RNA-small molecule interaction. As stated at the top of page 3, he presents "evidence indicating that attractive and repulsive forces present in the critical region of the minor groove of RNA dictate or define the geometrical constraints of the region. These forces, as described in the specification, and below, define the structure of the critical region in a way that provides one with a mental picture of a defined "space" that can only be accessed by a compound of the correct "shape". He also reviews each of the claimed structural features: the hydrophobic environment of the minor groove, the hydrogen bonding, the electrostatic interactions, and the geometic and steric constraints. Dr. Williamson refers to the precedent of compounds that bind to DNA molecules (recognizing that here, the invention is the discovery that the minor groove of RNA is the critical binding site, whereas in DNA it is the major groove), as published by Dervan, et al., in Science 232, 464-471 (1986). Dr. Williamson also provides evidence that the claimed method and compounds are enabled and clearly described in view of his own subsequent work, published in part by Sultan, et al., Science 288, 107-112 (2000) and as demonstrated by the attached figures.

This evidence clearly support applicant's position that the specification and claims meet the requirements under 35 U.S.C. §112, written description.

D. Summary

An understanding of nucleic acid structure is the result of a detailed analysis of the molecular interactions between proteins and their target nucleic acid (i.e. the hydrogen bonding arrangements and hydrophobic interactions between, for example, repressors and target sequence). One of skill in the art will recognize that, in view of the present specification, the identification of the critical region of the target RNA sequence dictates and defines the specific conformation and the "order" of complementary groups on the compound that must be assembled in order to recognize the target RNA region.

The present specification shows at page 38, as pointed out by the Examiner, that the compounds which specifically inhibit the function of the targeted RNA are synthesized using methods known to those skilled in the art based upon the sequence and structure of the minor groove of the RNA. The specification also clearly describes the structure of the claimed compounds in view of the detailed description of the targeted minor groove of RNA that provide the geometric, spatial, hydrophobic, and hydrogen bonding constraints required for the claimed complementary compound to bind to a specific critical region and inhibit the RNA function.

As discussed in the accompanying declarations under 37 C.F.R. § 1.132, the geometric configuration of the target minor groove of RNA is predicated by the presence of hydrogen bonds, the hydrophobicity of the local environment, and "the repulsive and attractive forces that

exist as electrostatic entities". Each of these target RNA attributes is described in the specification. For example, the extensive stacking and base pairing of planar aromatic purines and pyrimidines inherently rendering the local environment inaccessible to solvent (or hydrophobic) is taught at page 2, lines 21-29. Furthermore, as disclosed at page 7, lines 24-26 (and again at pages 19 and 20), a network of hydrogen bonds provides not only for a stable structure within the minor groove, but also the establishment of a proper interface between compounds and their target nucleic acid (can be visualized as two pieces of a puzzle that fit together, wherein the properly spaced and oriented hydrogen bonds of the compound line the edge of one puzzle piece, and the accessible hydrogen bonds of the target RNA line the edge of the complementary piece). The maximization of these properties strengthens the electrostatic interaction between the compound and its target RNA. The end result is a specific (complementary) binding interaction that is dependent upon the defined compound structure as claimed and described.

It should be noted that Applicant is *not* claiming support for defining the structural features of the claimed compound based solely upon the functionality of "hybridizing" a compound to an RNA molecule. Applicant realizes that the Guidelines do not provide that a compound be defined *only* by its function. Each *physical* characteristic of the target RNA molecule, as described in the specification and further supported by the declarations submitted herewith, contributes to the claimed complementarity of the inhibitory compounds, and therefore their structure. The formation of a complementary interface between the target RNA and the

claimed compound is based upon, *inter alia*, the recognition of specific and accessible hydrogen bonds. This interface lies at the core of the presently claimed composition because it precisely defines the compound for which the target RNA will accept as its "partner".

While most, if not all, compounds that bind RNA do have hydrogen bonding sites, only a few will have the necessary pattern of sites to be utilized specifically by the targeted critical region. The definition of the critical region within the minor groove by a combination of primary, secondary and tertiary structure analysis, as recited in claim 11, determines the structure of the claimed compounds. Therefore, in view of the specification and the submitted declarations under 37 C.F.R. § 1.132, the structural features common to the claimed compound, as defined by the term "complementary" and by containing the requisite hydrogen bonding acceptor and donor sites, are clearly described.

In summary, Applicant has not only described significant structural and physical properties of the claimed compound and its cognate RNA target, Applicant has additionally submitted two independent expert opinions that clearly support this assertion and describe the specification as being sufficient for one of ordinary skill in the art to realize the *structural* features that *define* the claimed compound.

Allowance of all claims 1 and 3-21 is earnestly solicited.

Respectfully submitted,

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APPENDIX: Claims As Pending

1. A method for designing a compound specifically inhibiting targeted ribonucleic acid function comprising the steps of:

(a) determining the nucleotide sequence in the targeted ribonucleic acid that is critical to function;

(b) determining the secondary structure of the region of the targeted ribonucleic acid in which the critical site is located;

(c) determining the three-dimensional structure of the targeted RNA, including the position of the critical site relative to the major and minor grooves;

(d) determining the sequence of nucleotides and structure flanking the critical site in the targeted ribonucleic acid that is specific to the critical region of the ribonucleic acid to be inhibited and within the minor groove; and

(e) synthesizing a compound that will bind specifically to the critical site within the minor groove of the targeted ribonucleic acid thereby inhibiting targeted ribonucleic acid function.

3. The method of claim 1 wherein the ribonucleic acid is selected from the group consisting of mRNA, rRNA, tRNA and viral RNA.

4. The method of claim 1 wherein inhibition of targeted ribonucleic acid function inhibits protein synthesis.

5. The method of claim 4 wherein protein synthesis is inhibited in cells selected from the group consisting of tumor cells, virally infected cells, and bacterial cells.

6. The method of claim 1 wherein the three-dimensional structure is modeled using sequences of the RNA and calculating the minimum energies for these structures.

7. The method of claim 1 wherein the critical region of the targeted ribonucleic acid is determined by mutation of regions of the targeted RNA and comparison of the function of the mutated RNA with the original RNA, wherein mutations that result in mutant RNA having altered function indicate that the site of mutation is a critical site.

8. The method of claim 1 wherein the targeted RNA is a tRNA, wherein the critical region of the tRNA is determined by site directed mutation of the tRNA and analysis of the function of the mutated tRNA.

9. The method of claim 1 further comprising determining an effective amount of the compound and combining the compound with a pharmaceutical carrier.

10. The method of claim 9 wherein the carrier is selected from the group consisting of pharmaceutically acceptable compositions for topical administration, pharmaceutically acceptable compositions for parenteral administration, pharmaceutically acceptable compositions for enteral administration, and combinations thereof.

11. A complementary compound comprising hydrogen bond donor and acceptor sites arranged to specifically bind and inhibit the function of a targeted RNA molecule, wherein the compound is specifically directed to and binds to a critical region of the RNA molecule, located within the minor groove of the RNA molecule, identified by a combination of the primary, secondary and tertiary structure of the critical region.

12. The complementary compound of claim 11 wherein the RNA is selected from the group consisting of mRNA, tRNA, rRNA, and viral RNA.

13. The complementary compound of claim 11 further comprising a pharmaceutically acceptable carrier selected from the group consisting of pharmaceutically acceptable compositions for topical administration, pharmaceutically acceptable compositions for parenteral administration, pharmaceutically acceptable compositions for enteral administration, and combinations thereof.

14. The method of claim 3 wherein the critical site is in the minor groove of the acceptor stem of a tRNA molecule.

15. The method of claim 14 wherein the tRNA molecule is $tRNA^{Ala}$.

16. The method of claim 15 wherein the critical site is the G3:U70 base pair.

17. The complementary compound of claim 12 wherein the compound binds to a critical region within the minor groove of the acceptor stem of a tRNA molecule.

18. The complementary compound of claim 17 wherein the tRNA molecule is $tRNA^{Ala}$.

19. The complementary compound of claim 17 wherein the critical region is the G3:U70 base pair.

20. The method of claim 1 wherein the compound is a nucleic acid and the compound is synthesized *in vivo* from a retroviral vector.

21. The complementary compound of claim 11 wherein the compound is a nucleic acid and the compound is synthesized *in vivo* from a retroviral vector.